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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,172	09/29/2003	Stephen Donovan	17510DIV2 (BOT)	5916

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,172	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/04 & 9/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the Restriction requirement filed on May 25, 2005 is acknowledged. Applicant's election of Group II, with traverse, claims 22-30 is acknowledged. Claims 1-21 have been cancelled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 22 and 26-29 are rejected under 35 U.S.C. 102(e) as anticipated by Yuzhakov et al *(U.S. Patent No. 6,565, 532 B1 published May 20, 2003).*

Claims 22 and 26-29 are drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum, and (b) applying botulinum toxin to the skin of the patient in an area that has had the stratum corneum disrupted by step (a).

Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing

a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition, which comprises a botulinum (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5). Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" is taught in the prior art reference. The claim limitation " wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures" would be inherent in the teachings of the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 22 and 25-29 are rejected under 35 U.S.C. 103(a) as unpatentable over in view of Yuzhakov et al *(U.S. Patent No. 6,565, 532 B1 published May 20, 2003)* in view of Mitragotri et al *(Science, Vol. 269, August 11, 1995).*

Claims 22 and 25-29 are drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum, and (b) applying botulinum toxin to the skin of the patient in an area that has had the stratum corneum disrupted by step (a).

Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum (column 51, lines 56-63) and

an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5). Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" is taught in the prior art reference.

Yuzhakov et al do not teach disrupting the stratum corneum by applying ultrasound at a frequency between 20 kHz and less than 10 Mhz at an intensity that does not permanently damage the patient's skin.

Mitragotri et al teach that ultrasound can mediate transdermal protein delivery by increasing the permeability of the human skin (see the Title and the Abstract). Mitragotri et al teach that low frequency ultrasound can induce significant transdermal transport of proteins including proteins between molecular weights of 6,000 and 48,000 (page 850). Mitragotri et al teach that application of ultrasound at therapeutic frequencies of about 1 MHz induces growth and oscillations of air pockets in the stratum corneum of human skin (page 850).

It would be *prima facie* obvious at the time the invention was made to use ultrasound to increase the permeability of the human skin because Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate for drug delivery and

Mitragotri et al teach that low frequency ultrasound can induce significant transdermal transport of proteins including proteins between molecular weights of 6,000 and 48,000 (page 850). It would be expected barring evidence to the contrary, that the use of ultrasound at therapeutic frequencies would be effective in increasing the permeability of the human skin.

4. Claims 22-29 are rejected under 35 U.S.C. 103(a) as unpatentable over in view of Yuzhakov et al and Mitragotri et al as applied to claims 22, 25-29 above and further view of Smith *(U.S. Patent 5,587, 396 published December 24, 1996).*

Claims 23 and 24 are drawn to a method of reducing neurotransmitter release, wherein the stratum corenum is disrupted by abrasively removing the stratum corneum. The teachings of Yuzhakov et al and Mitragotri et al have been described above.

Yuzhakov et al and Mitragotri et al do not teach disrupting the stratum corneum by abrasively removing the stratum corneum.

Smith teaches that tape stripping is an effective barrier disruption method (column 16). Smith teaches that tape stripping vary widely with different individuals (column 16).

It would be *prima facie* obvious at the time the invention was made to abrasively disrupt the stratum corneum (e.g. tape stripping) because Smith teaches that tape stripping is an effective barrier disruption method and Yuzhakov et al teach small pressure of the microneedle arrays through the stratum corneum of the skin can delivery of drugs or facilitate biological fluid sampling (column 4). Yuzhakov et al teach

that drugs can be deliver by way of passive diffusion (column 4). It would be expected barring evidence to the contrary, that the use of tape stripping would be effective in increasing the permeability of the human skin and thereby facilitating drug delivery.

5. Claims 22 and 26-30 are rejected under 35 U.S.C. 103(a) as unpatentable over in view of Yuzhakov et al *(U.S. Patent No. 6,565, 532 B1 published May 20, 2003)* in view of Cevc *(U.S.Patent No. 6, 165, 500 published December 26, 2000).*

Claims 22 and 26-30 are drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum, and (b) applying botulinum toxin to the skin of the patient in an area that has had the stratum corneum disrupted by step (a).

Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5). Yuzhakov et al teach that the drug delivery portion of this

invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" is taught in the prior art reference.

Yuzhakov et al do not teach a method of reducing neurotransmitter release in a subdermal structure of a patient, wherein the botulinum toxin is incorporated into a transfersome.

Cevc teaches transfersome compositions comprising agents such as botulinum toxin D (column 31). Cevc teaches that the transfersome compositions of the invention can be introduced not only to a permeability barrier such as the skin, but moreover, can be transported into deeper tissues when they become systemically active (column 4, 66-67 and column 5, lines 1-4).

It would be *prima facie* obvious at the time the invention was made to use incorporated botulinum toxin into transfersomes as taught by Cevc because Cevc teaches that the transfersome compositions of the invention can be introduced to a permeability barrier such as the skin and can also be transported into deeper tissues when they become systemically active. It would be expected barring evidence to the contrary, that botulinum toxin compositions incorporated into transfersomes is a effective method of delivering botulinum toxin to skin thereby reducing neurotransmitter release in a subdermal structure in a patient.

Status of Claims

6. No claims allowed.

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
July 17, 2005

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